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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/061,417	04/16/1998	ERIC N. OLSON	UTSD:548	1649

7590 03/18/2004

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/061,417	OLSON ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1, 4, 9 are being examined.

The following are the remaining rejections.

DECLARATION

The Declarations by Erik Bush, Beverly Rothermel Williams and R. Sander Williams submitted on 07/09/2003 are acknowledged and entered.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Rejection under 35 USC 112, first paragraph of claims 1, 4, 9 pertaining to lack of a clear written description of an inhibitor of NF-AT3 function, including a small molecule inhibitor remains for reasons already of record in paper No.26.

Applicant submits the Declaration by Erik Bush.

In the Declaration by Erik Bush, in item 8, it was recited that a small molecule, compound #15 increases the expression of a calcineurin inhibitory protein (MCIP) in vitro in cultured rat neonatal ventricular myocytes (Item 8).

It is noted that the structure of said compound #15 is not known, in view that the attached figure A is not found, which is supposed to be attached to the Declaration, and that it is not clear whether figure A contains the structure of compound #15. It is further noted that one cannot determine whether compound # 15 is an inhibitor of NF-ATF3,

because increasing the expression of a calcineurin inhibitory protein (MCIP) in vitro in cultured rat neonatal ventricular myocytes by compound # 15 does not correlate with inhibition of NF-AT3, nor treating hypertrophy, which are completely different phenomena.

Item 9 of the Declaration recites that another small molecule, compound # 18 increases the expression of a different isoform of MCIP, and strongly promotes cardiomyocyte growth.

It is noted that the structure of said compound #18 is not disclosed. It is further noted that one cannot determine whether compound # 18 is an inhibitor of NF-ATF3, because increasing the expression of an isoform of calcineurin inhibitory protein (MCIP) does not correlate with inhibition of NF-AT3, nor treating hypertrophy, which are completely different phenomena.

Applicant argues as follows:

Knowledge of actual binding sites and exhaustive listing of structure, such as structure of GATA4 mimetics, antisense molecules, or competitive inhibitors of NF-AT3, are not required. Moreover, as discussed in the declaration of Dr. Rick Gorczmski, those of skill in the art would not doubt that GATA4 does indeed bind to NF-AT3, nor would they challenge the notion that interference with that interaction will have inhibitory effects on NF-AT3'S ability to activate gene transcription of hypertrophic genes, such interference clearly being mediated by any of the molecules or agents listed above or referenced in the specification.

Applicant further argues that a number of the NF-AT3 targeting molecules disclosed by Applicant are already known, and the molecules such as GATA4 mimetics, antisense molecules are defined by the prior art structure of the target molecules.

Applicant asserts that the claimed molecules are shown to interact, or can be proven with little experiment to interact with NF-AT3.

Applicant asserts that Applicant is not aware that commonality of structure is required for claiming a genus of inhibitors.

Applicant's arguments set forth in paper of 10/27/03 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that other than cyclosporin A and DTC's, which have uncommon structure, and which are not GATA4 mimetics, antisense molecules, the structure of GATA4 mimetics, antisense molecules, or competitive inhibitors of NF-AT3 is not disclosed in the specification, or in the art. Moreover, the molecules such as GATA4 mimetics, antisense molecules are not defined by the prior art structure of the target molecules, because the configuration of the second zinc finger of GATA4 is not disclosed, and because which antisense molecules that could inhibit NF-AT3 in vivo are not disclosed, and it would require a potential method for isolating them.

The following teaching in the court clearly applies to the claimed invention. The court has held that statements in the specification describing the functional characteristics of a DNA molecule or methods of its isolation do not adequately describe a particular claimed DNA sequence. Instead "an adequate written description of DNA requires more than a mere statement that it is part of the invention and reference to a

potential method for isolating it; what is required is a description of the DNA itself." Id. at 1566-67 (quoting Fiers, 984 F.2d at 1171).

The instant specification may provide an adequate written description of the claimed inhibitors of NF-AT3, per Lilly by structurally describing a representative number of inhibitors of NF-AT3, or by describing structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the inhibitors of NF-AT3 required to practice the method of claims 1, 4, 9 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any inhibitors of NF-AT3 other than cyclosporin A, and DTC's as provided in Applicant response, both of which are known in the art, and having completely uncommon structure, nor any physical or chemical characteristics of the inhibitors of NF-AT3, other than cyclosporin A, and DTC's, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification and Applicant response disclose two inhibitors of NF-AT3, cyclosporin A, and DTC's, this does not provide a description of the broadly claimed inhibitors of NF-AT3 that would satisfy the standard set out in Enzo.

The specification also fails to describe the inhibitors of NF-AT3, by the test set out in Lilly. The specification and Applicant response describe only two inhibitors of NF-AT3. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Thus, the specification does not provide an adequate written description of the inhibitors of NF-AT3 that is required to practice the claimed invention. Since the specification fails to adequately describe the product for use in the claimed method of treating hypertrophy, it also fails to adequately describe the claimed method of treating hypertrophy.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph of claims 1, 4, 9 pertaining to lack of enablement of a method for treatintg hypertrophy, using any inhibitors of NF-AT3, including a small molecule inhibitor, remains for reasons already of record in paper No.26.

Applicant submits the Declaration by Erik Bush.

In the Declaration by Erik Bush, in item 8, it was recited that a small molecule, compound #15 increases the expression of a calcineurin inhibitory protein (MCIP) in vitro in cultured rat neonatal ventricular myocytes (Item 8).

It is noted that the structure of said compound #15 is not known, in view that the attached figure A is not found, which is supposed to be attached to the Declaration, and that it is not clear whether figure A contains the structure of compound #15. It is further noted that one cannot determine whether compound # 15 is an inhibitor of NF-ATF3, because increasing the expression of a calcineurin inhibitory protein (MCIP) in vitro in cultured rat neonatal ventricular myocytes by compound # 15 does not correlate with inhibition of NF-AT3, nor treating hypertrophy, which are completely phenomena.

Item 9 of the Declaration recites that another small molecule, compound # 18 increases the expression of a different isoform of MCIP, and strongly promotes cardiomyocyte growth.

It is noted that the structure of said compound #18 is not disclosed. It is further noted that one cannot determine whether compound # 18 is an inhibitor of NF-ATF3, because increasing the expression of an isoform of calcineurin inhibitory protein (MCIP) does not correlate with inhibition of NF-AT3, nor treating hypertrophy, which are completely different phenomena.

In addition, it is noted that Applicant's arguments concerning 1) transfected mice and transgenic mice that are not representative of what would be found in human subjects, and thus not enabling for in vivo use in patients, and 2) how to make and use the claimed method using the small molecule single chain antibodies, are not issues raised by the new rejection, and thus are not addressed here.

Concerning the issues of how to make and use the GATA4 mimetics, Applicant has not answered to these issues. Sufficient guidance is not provided in the specification for the reasons set forth previously and above.

Concerning the issue of the unpredictability of successful in vivo use of antisense inhibitors of NF-AT3, Applicant argues as follows:

Applicant recites Bennett et al, 1998, which states that antisense oligonucleotides are widely used as tool to explore the pharmacological effects of inhibiting expression of a selected gene products" and, that with careful selection, proper controls, and careful dose-response curves antisense oligonucleotides, it is possible to utilize effective research tools and potèntially as therapeutic agents." Applicant argues that these statements, made at the time of filing, directly contradict the statements of Gura, made 3 years before filing, that the Examiner uses to prove that antisense technology is and was unpredictable.

The recitation of Bennett et al is acknowledged.

Applicant's arguments set forth in paper of 10/27/03 have been considered but are not deemed to be persuasive for the following reasons:

Contrary to Applicant's arguments, Bennett et al do not contradict the teaching of Gura et al. It is noted that based on the teaching of Bennett et al, antisense oligonucleotides are only research tools and potentially (emphasis added) therapeutic agents, and thus the unpredictability of antisense gene therapy, including the difficulty in targeting the antisense to the desired tissues would still be applicable at the time the invention was made and at the present time, eventhough the reference by Gura is 3

years older than that of Bennett et al. Further, the unpredictability of antisense gene therapy is further overwhelmingly confirmed by the teaching of Miller et al, 1995, Deonarain et al, 1998, Verma et al, 1997, and Crystal et al, 1995, all of record.

REJECTION UNDER 35 USC 102(b)

Claim 1 remains rejected under 35 USC 102(b) as being anticipated by Haverich et al, or Ried et al, as evidenced by McCaffrey et al, and Martinez-Martinez et al, for reasons already of record in paper No.26.

Applicant argues as follows:

Applicants assert that every element in claim 1 is not found in any of the prior art references. Claim 1 teaches treatment of hypertrophy by inhibiting the function of NT-AT3 in a cardiomocyte using a compound that inhibits the function of NF-AT3. The Haverich and Reid references teach the use of cyclosporin A (CsA) for treatment of transplantation disease; they do not teach, much less suggest treatment of hypertrophy or effects on cardiac structure. They are instead directed towards improving cardiac function in a post-transplant environment. Additionally, while the Mccaffrey and Martinez-Martinez references do teach that CsA is an NF-AT3 inhibitor, they do not teach the use of an NF-AT3 inhibiting compound to treat hypertrophy. Not one of these references teaches the invention, nor do the collection of them inherently predict or assert the invention.

Applicant asserts that the Examiner points to Ex parte Novitski to support an inherency argument, and argues that applicants have not addressed this citation. This is

untrue. Novitski merely states that inherent anticipation may lie, that claims are interpreted as broadly as reasonably possible, and that limitations are not read into the claims.

Applicant asserts that however, a limitation of the instant claims is treating cardiac hypertrophy. Thus, nothing must be read into the claims, and the claims cannot be read to exclude this limitation.

As pointed out before, applicants submit that the case law requires that an inherent disclosure "must be certain". Ex parte Mcoueen, 123 USPQ 37 (Bd. App. 1958). There is no evidence from the cited references that hypertrophy had been treated or even analyzed. The prior art specifically deals with transplantation disease and cardiac function after transplant in response to CsA application.

Transplantation disease has not and is not defined as cardiac hypertrophy, and it is possible to have one without the other, thus, there cannot be any inherency. The references do not teach a treatment for hypertrophy nor would one of skill in the art be expected to infer from these references that CsA, and subsequently NF-AT3 inhibitors, were being used to treat hypertrophy. The examiner has not even attempted to address this issue, instead merely repeating the previous rejection.

Applicant's arguments set forth in paper of 10/27/03 have been considered but are not deemed to be persuasive for the following reasons:

The claimed method steps and the target composition do not have the limitation that the treated cardiomyocyte is hypertrophic. Thus as stated in the previous Office action, the claimed target composition is cardiomyocyte, which is the same treated

composition as that taught by prior art. Further, the claimed method steps are exactly the same as method steps taught by prior art, i.e. inhibiting the function of NF-AT3 in a cardiomyocyte, which reads on administering an agent that inhibits the function of NF-AT3 in a cardiomyocyte.

Because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

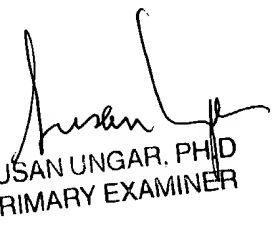
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, YVONNE EYLER can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



MINH TAM DAVIS

March 10, 2004